Mechanical Thrombectomy in Ischemic Stroke Patients With Alberta Stroke Program Early Computed Tomography Score 0–5

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Background and Purpose—If anterior circulation large vessel occlusion acute ischemic stroke patients presenting with ASPECTS 0–5 (Alberta Stroke Program Early CT Score) should be treated with mechanical thrombectomy remains unclear. Purpose of this study was to report on the outcome of patients with ASPECTS 0–5 treated with mechanical thrombectomy and to provide data regarding the effect of successful reperfusion on clinical outcomes and safety measures in these patients.

Methods—Multicenter, pooled analysis of 7 institutional prospective registries: Bernese-European Registry for Ischemic Stroke Patients Treated Outside Current Guidelines With Neurothrombectomy Devices Using the SOLITAIRE FR With the Intention for Thrombectomy (Clinical Trial Registration—URL: https://www.clinicaltrials.gov. Unique identifier: NCT03496064). Primary outcome was defined as modified Rankin Scale 0–3 at day 90 (favorable outcome). Secondary outcomes included rates of day 90 modified Rankin Scale 0–2 (functional independence), day 90 mortality and occurrence of symptomatic intracerebral hemorrhage. Multivariable logistic regression analyses were performed to assess the association of successful reperfusion with clinical outcomes. Outputs are displayed as adjusted Odds Ratios (aOR) and 95% CI.

Results—Two hundred thirty-seven of 2046 patients included in this registry presented with anterior circulation large vessel occlusion and ASPECTS 0–5. In this subgroup, the overall rates of favorable outcome and mortality at day 90 were 40.1% and 40.9%. Achieving successful reperfusion was independently associated with favorable outcome (aOR, 5.534; 95% CI, 2.363–12.961), functional independence (aOR, 5.583; 95% CI, 1.964–15.873), reduced mortality (aOR, 0.180; 95% CI, 0.083–0.390), and lower rates of symptomatic intracerebral hemorrhage (aOR, 0.235; 95% CI, 0.062–0.887). The mortality-reducing effect remained in patients with ASPECTS 0–4 (aOR, 0.167; 95% CI, 0.056–0.499). Sensitivity analyses did not change the primary results.

Conclusions—In patients presenting with ASPECTS 0–5, who were treated with mechanical thrombectomy, successful reperfusion was beneficial without increasing the risk of symptomatic intracerebral hemorrhage. Although the results do not allow for general treatment recommendations, formal testing of mechanical thrombectomy versus best medical treatment in these patients in a randomized controlled trial is warranted. **(*Stroke*. 2019;50:880-888. DOI: 10.1161/STROKEAHA.118.023465.)**

Key Words: infarction ■ magnetic resonance imaging ■ reperfusion ■ selection for treatment ■ thrombectomy ■ tomography

Whether mechanical thrombectomy is beneficial in ischemic stroke patients presenting with low ASPECTS (Alberta Stroke Program Early CT Score) remains uncertain, because only a few of these patients were enrolled in the recent pivotal thrombectomy trials.[1,2] Correspondingly, the current American Stroke Association /American Heart Association

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guidelines do not include an unambiguous recommendation to treat patients with ASPECTS 0–5, but rather state that mechanical thrombectomy may be considered in these patients.[3] Patients with low ASPECTS are at higher risk of symptomatic intracerebral hemorrhage (sICH)[4–7] and the proportion of salvageable tissue is small, which explains the overall low rate of good functional outcomes in this subgroup.[1]

Previous studies suggested that successful reperfusion may be beneficial to patients with diffusion-weighted ASPECTS 0–5 or 0–6, respectively.[8–10] The aim of the present study was to analyze the effect of successful reperfusion on functional outcome, mortality and sICH in patients presenting with ASPECTS 0–5 who were included in the Bernese-European Registry for ischemic stroke patients treated Outside current guidelines with Neurothrombectomy Devices using the SOLITAIRE FR With the Intention For Thrombectomy (BEYOND-SWIFT) registry. Furthermore, safety and efficacy of endovascular treatment in this subgroup was assessed in comparison to a group of patients presenting with ASPECTS 6–10.

Methods

BEYOND-SWIFT Registry

BEYOND-SWIFT was a retrospective, international, multicenter observational registry. The participating centers contributed records of consecutive acute ischemic stroke patients, who were treated with a CE-labeled market-release neurothrombectomy device manufactured by Medtronic (Dublin, Ireland). Further information on the registry and participating centers can be found in Information I and Table I in the online-only Data Supplement.

The centers provided 2047 patient datasets, of whom 1 missed baseline characteristics such as age, sex, and admission National Institutes of Health Stroke Scale (NIHSS). Consequently, a total of 2046 patients were included into the registry. Most patients included in the BEYOND-SWIFT registry were treated for large-vessel occlusion (intracranial ICA, M1, and M2) anterior circulation strokes (n=1820). Of these, 1630 had documented 90-day follow-up including 1532 with records of preinterventional ASPECTS. Two-hundred-thirty-seven patients presented with ASPECTS 0–5 (Figure 1 for study flowchart). Data gathered within the framework of this registry will be made available for replication or further collaboration on request to Prof. Dr Urs Fischer and after clearance by the local ethics committee in Bern.

Variables and Image Analysis

The site of occlusion was categorized into intracranial internal carotid artery, carotid-T/L, M1, M2, and M3 segments of the middle cerebral artery, A1 and A2 segment of the anterior cerebral artery, vertebral artery, basilar artery, P1 and P2 segment of the posterior cerebral artery based on the diagnostic admission imaging (computed tomography angiography/magnetic resonance angiography). For 7 patients, no data on occlusion site was provided. Postprocedural Thrombolysis in Cerebral Infarction (mTICI) scale was operator adjudicated at each center or rated by an independent research fellow, depending on the applicable institutional standards (Table I in the online-only Data Supplement). TICI 2b was rated as reperfusion of at least 50% of the initially occluded target territory, according to the modified version of the TICI scale.[11] ASPECTS was evaluated at each site (Table I in the online-only Data Supplement) and was based on admission CT in 910/1532 cases of anterior large-vessel occlusion. In 600 cases, ASPECTS was rated on diffusion-weighted magnetic resonance imaging, and in 22 cases, no information on the admission imaging modality was provided. Functional clinical outcome was evaluated using the modified Rankin Scale (mRS) at 90 days, which was evaluated by a physician or a trained and certified mRS nurse usually not involved into acute treatment of the patient (Table I in the online-only Data Supplement). All participating centers evaluated the mRS on routinely scheduled and standardized telephone interviews or clinical visits. Neurological symptoms on admission and 24 hour after the intervention were evaluated by a stroke neurologist applying the NIHSS.

Statistical Analysis

For the present analysis, a protocol with predefined outcome variables was written before analysis or inspection of the data began (https://clinicaltrials.gov/ProvidedDocs/64/NCT03496064/SAP_000.pdf). The primary end point of this analysis was mRS score 0–3 (favorable outcome) at day 90.[12] Secondary and safety outcomes consisted of mRS score 0–2 (functional independence) at day 90, major early neurological improvement (defined as admission NIHSS—24h NIHSS ≥8 or 24h NIHSS <1),[13] all-cause mortality at day 90, and sICH.

Univariate comparisons were made using standard statistical measures (Fisher exact test for categorical variables, Mann–Whitney *U* test for nonnormally continuous, or ordinally scaled variables and Welsch *t* test for normally distributed data). Association of successful reperfusion with all outcome parameters was assessed using multivariable logistic regression adjusting for the following prespecified confounders: age, sex, NIHSS on admission, tandem versus nontandem (tandem defined as >90% cervical stenosis or cervical occlusion), center (categorical, contrast type: indicator, comparator: largest center), ASPECTS ≤3 versus ASPECTS 4–5, intravenous thrombolysis, risk factor hypertension, dyslipidemia, smoking, previous stroke, diabetes mellitus, in-hospital stroke, type of admission imaging, intracranial ICA/carotid-T versus M1/M2. For sensitivity purposes, analyses were rerun either with confinement to a cohort presenting with ASPECTS 0–4 or with implementation of the following interaction terms:

1. Successful reperfusion (1: successful) * admission modality (1: CT).
2. Successful reperfusion (1: successful) * age ≤70 years versus >70 years (1: age≤70).

In a final sensitivity analysis, diffusion-weighted imaging (DWI) ASPECTS were increased by 1 point to estimate corresponding CT-ASPECTS as suggested by findings derived from the SAMURAI registry.[6] Thereafter, the population of ASPECTS 0–5 was recalculated and analyses were rerun. This analysis was added to the statistical analysis plan after protocol finalization and data inspection.

Results

Of 1532 patients included into the present analysis, 237 patients presented with ASPECTS 0–5, whereas 1295 patients had an ASPECTS >5. Distribution of ASPECTS by admission imaging modality is shown in Figure IA in the online-only Data Supplement.

Study Cohort ASPECTS 0–5

Mean age of patients presenting with ASPECTS 0–5 (N=237), was 67.1±14.4 years and 43.5% (N=103) were female. Of these 237 patients, 93 presented with ASPECTS 5, 60 with ASPECTS 4, and 84 with ASPECTS 0–3. ASPECTS distribution by imaging modality within the subcohort of ASPECTS 0–5 is shown in Figure IB in the online-only Data Supplement. Patients presented with severe neurological deficits (median NIHSS 18; interquartile range [IQR] 15–22) and were admitted to the hospital with a median delay from symptom-onset/last-seen-well to admission of 173 minutes (IQR, 85–278 minutes; available for N=190). Successful reperfusion was achieved in 69.9% (N=165/236, 1 patient had missing information on reperfusions status) patients, with a median groin-puncture to

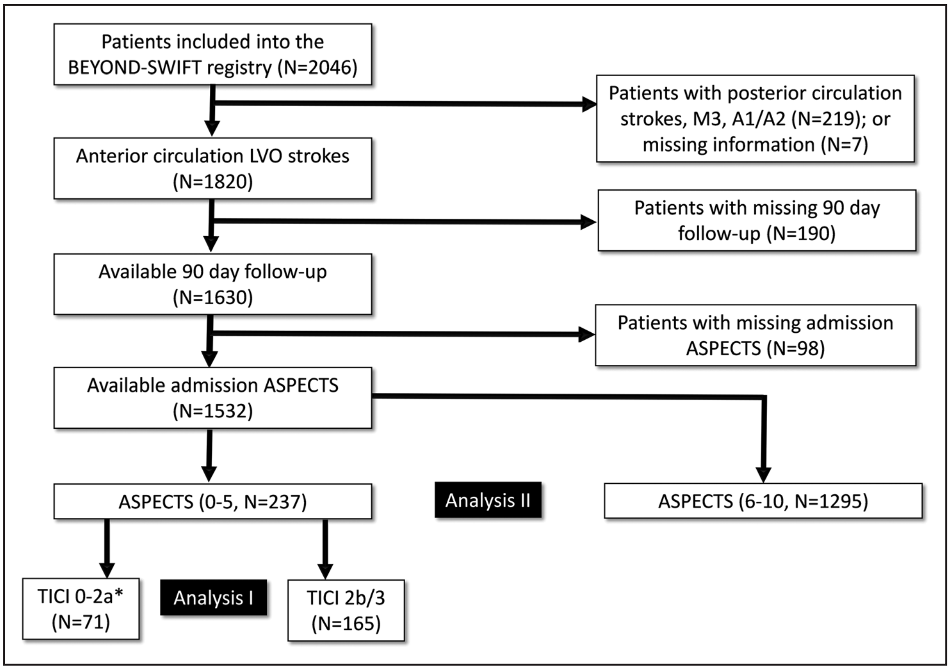

Figure 1. Registry flowchart. ASPECTS indicates Alberta Stroke Program Early CT Score; BEYOND-SWIFT, Bernese-European Registry for Ischemic Stroke Patients Treated Outside Current Guidelines With Neurothrombectomy Devices Using the SOLITAIRE FR With the Intention for Thrombectomy; LVO, large-vessel occlusion; and TICI, Thrombolysis in Cerebral Infarction. *One patient was excluded from the comparison of TICI 0-2a with TICI 2b/3 because of missing data regarding the final reperfusion success.

TICI 2b interval of 48 minutes (IQR, 30–79; N=164). Overall rates of favorable outcome (mRS ≤3) and mortality at day 90 were 40.1% (N=95/237) and 40.9% (N=97/237). Early neurological improvement was observed in 21.2% (N=32) of 151 patients for whom 24 hours NIHSS was available. When comparing ASPECTS 0–5 patients with (study population, N=237) and without available follow-up (N=13), no systemic bias regarding the distribution of baseline characteristics could be noted (Table II in the online-only Data Supplement).

Reperfusion in Patients With ASPECTS 0–5

Within the cohort of patients presenting with ASPECTS 0–5, there was no difference in baseline characteristics, type of admission imaging, occlusion site, or stroke causes between successfully and unsuccessfully reperfused patients (*P*>0.05; Table 1). However, univariate comparison revealed a significantly superior outcome for successfully reperfused patients, as evidenced by all outcome variables (Table 1, Figure 2A, and Figure III in the online-only Data Supplement). The outcome difference was seen among patients selected by non-contrast CT (NCCT) and magnetic resonance imaging, although generally, patients selected by magnetic resonance imaging had better outcome profiles (Figure 2B). The effect was observable in patients with ASPECTS 5 and in patients with ASPECTS 4, but not in patients with ASPECTS 0–3 (Figure IV in the online-only Data Supplement). However, a tendency for a mortality reducing effect of successful reperfusion in ASPECTS 0–3 was found (47.4% versus 66.7%; *P*=0.108). After adjusting for the prespecified clinical confounders listed in the methods section, successful reperfusion was associated with favorable clinical outcome (mRS score, 0–3; aOR, 5.534; 95% CI, 2.363–12.961; Table 2, Figure V in the online-only Data Supplement), functional independence (mRS score, 0–2; aOR, 5.583; 95% CI, 1.964–15.873), major early neurological improvement (aOR, 11.635; 95% CI, 3.980–34.011), and reduced mortality (aOR, 0.180; 95% CI; 0.083–0.390). Furthermore, rates of sICH were lower in successfully reperfused patients (aOR, 0.235; 95% CI, 0.062–0.887). There was no interaction between type of imaging or age groups and effect of successful reperfusion in any of the above-mentioned analyses (Table 2). Results of the logistic regression output by strata of admission imaging modality are shown in Figure VI in the online-only Data Supplement. A significant effect of reperfusion was still observed for mRS score 0–3 and mortality in both subgroups, however, uncertainty increased considerably (especially for CT). In a subcohort of patients with successful reperfusion, achieving TICI 3 instead of only TICI 2b was found to result in additional benefit (Figure IV in the online-only Data Supplement). When analyses were confined to patients with ASPECTS 0–4 (N=144), the positive association between successful reperfusion and the outcome variables remained statistically significant only for mortality (aOR, 0.168; 95% CI, 0.056–0.499; Table 3 and Figure VII in the online-only Data Supplement). In a final sensitivity analyses, DWI-ASPECTS was increased by 1 point to estimate corresponding NCCT-ASPECTS and transferability to CT imaging in line with the findings observed in the SAMURAI registry (Stroke Acute Management With Urgent Risk-Factor Assessment and Improvement).[6] Analyses were rerun with N=172 patients with adjusted ASPECTS ≤5. Here, comparable results were obtained, except that the association between successful reperfusion and lower rates of sICH was nonsignificant (Table III and Figure VIII in the online-only Data Supplement).

Table 1. Comparison of Patients Presenting With ASPECTS 0–5 With and Without Successful Reperfusion

ASPECTS 0–5, N=237*	TICI 0-2a (N=71)	TICI 2b/3 (N=165)	*P* Value
Age	68.6±13.5	66.4±14.8	0.266
Sex, female	53.5% (38/71)	38.8% (64/165)	0.045
Admission NIHSS	19 (15–22, N=70)	18 (15–22, N=163)	0.636
In-Hospital Stroke	0% (0/71)	1.8% (3/165)	0.556
Symptom-onset/last-seen well to admission	180 (99–281, N=53)	170 (277–77, N=136)	0.274
Admission Imaging, MRI (N=231)	65.7% (46/70)	66.5% (107/161)	>0.999
IVT	36.6% (26/71)	47.3% (78/165)	0.153
Risk factors			
Smoking (N=233)	22.5% (16/71)	31.5% (51/162)	0.208
Hypertension (N=235)	70.4% (50/71)	63.4% (104/164)	0.370
Dyslipidemia (N=233)	56.5% (39/69)	55.5% (91/164)	>0.999
Previous CVE (N=234)	21.1% (15/71)	14.1% (23/163)	0.183
Occlusion site			0.373
iICA	2.8% (2/71)	7.9% (13/165)	
Carotid-T/L	32.4% (23/71)	30.3% (50/165)	
M1	63.4% (45/71)	58.2% (96/165)	
M2	1.4% (1/71)	3.6% (6/165)	
Tandem	16.9% (12/71)	18.2% (30/165)	0.855
Underlying cervical dissection	9.9% (7/71)	5.5% (9/164)	0.261
TOAST (N=233)			0.899
Large-artery	12.9% (9/70)	12.9% (21/163)	
Cardioembolism	30.0% (21/70)	35.0% (57/163)	
Other determined cause	8.6% (6/70)	8.0% (13/163)	
Unknown	48.6% (34/70)	44.2% (72/163)	
Outcome			
mRS score 0–3	13.7% (13/71)	49.7% (82/165)	<0.001†
mRS score 0–2	11.7% (7/71)	32.1% (51/165)	<0.001†
Delta NIHSS	0 (−10 to 2)	3 (0–8)	<0.001†
Major early neurological improvement (N=151)	4.8% (2/42)	27.5% (30/109)	0.002†
Mortality	63.4% (45/71)	30.9% (51/165)	<0.001†
sICH (N=236)	11.4% (8/70)	5.5% (9/165)	0.165

Data is displayed as mean±SD or median (interquartile range). ASPECTS indicates Alberta Stroke Program Early CT Score; Carotid-T/L, T- or L-type occlusion of the carotid terminus; CVE, cerebrovascular event; iICA, intracranial internal carotid artery; M1, first segment of the middle cerebral artery; M2, second segment of the middle cerebral artery; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; sICH, symptomatic intracerebral hemorrhage; TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

*For 1 patient, final reperfusion success was not available.

†$P<0.001$.

Procedural Efficacy, Safety, Complications, and Outcome Compared With Patients With ASPECTS 6–10

A comparison of baseline characteristics of patients with ASPECTS 0–5 versus patients with ASPECTS 6–10 indicated that patients treated with ASPECTS 0–5 were younger, more often had proximal occlusion patterns and more commonly presented with underlying cervical artery dissection (Table VI in the online-only Data Supplement). Patients presenting with ASPECTS 0–5 had lower rates of successful reperfusion (69.9% versus 83.9%; $P<0.001$) and time from groin puncture to reperfusion was longer (median, 53 minutes; IQR, 33–85 minutes versus median 45 minutes; IQR, 30–74 minutes; $P=0.009$). Median number of maneuvers did not differ between the 2 groups (median, 2; IQR, 1–3 versus 2; IQR, 1–3; $P=0.298$; data available for N=1087). Relative frequency of TICI 3 was comparable (49.7% versus 55.2%; $P=0.208$) in patients in whom reperfusion was successful (TICI ≥2b,

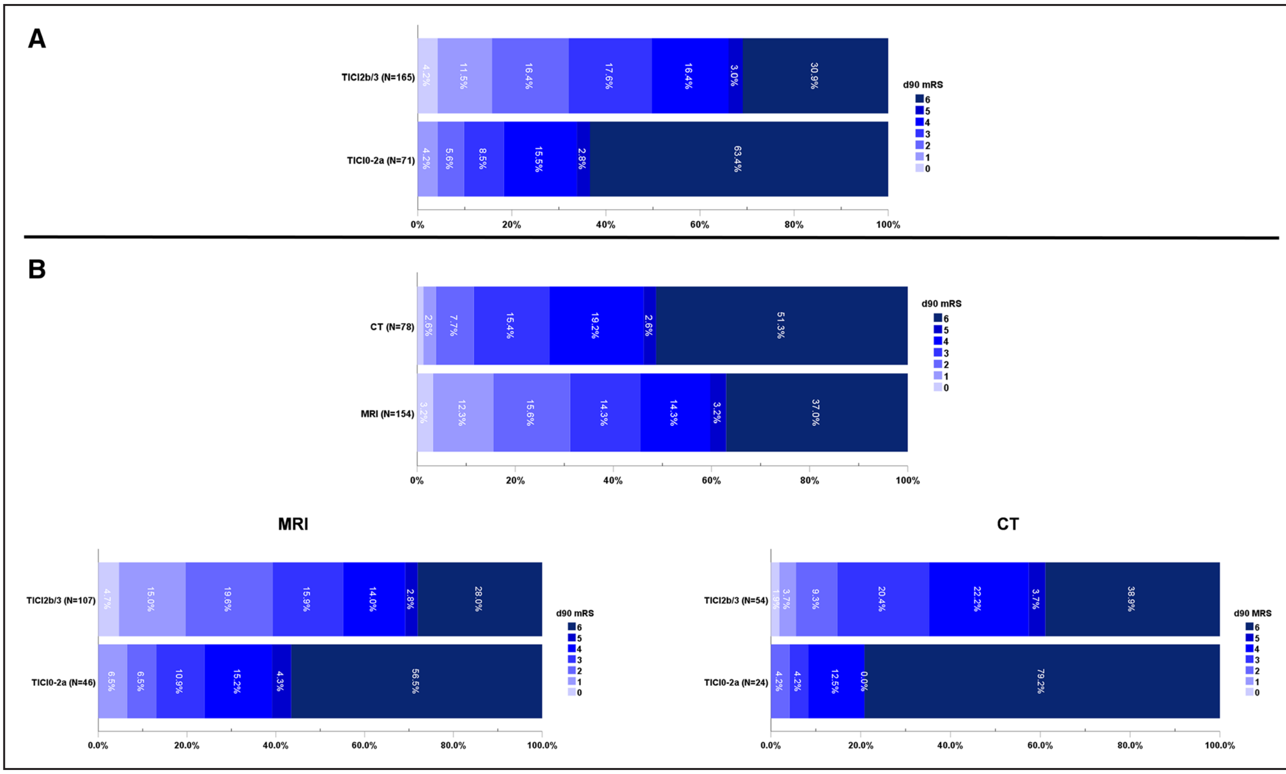

Figure 2. Modified Rankin Scale (mRS) of patients with ASPECTS 0–5 (Alberta Stroke Program Early CT Score; N=237) stratified according to reperfusion success. **A**, Mortality was shifted towards higher rates of mRS score 0–3, rather than increasing mRS score 4–5. Shift was significant for mRS score 0–3 (49.7% vs 13.7%; *P*<0.001) and mortality (30.9% vs 63.4%; *P*<0.001). One patient was not included owning to missing data regarding the postinterventional reperfusion quality (N=1/237). **B**, Favorable outcome was more often observed in patients selected by magnetic resonance imaging (MRI) diffusion-weighted imaging (DWI-ASPECTS) than in patients selected by CT (45.5% vs. 26.9%; *P*=0.007). Furthermore, moratlity was higher in patients selected by CT (51.3% vs 37.0%; *P*=0.048). In both, MRI and computed tomography (CT)-selected patients, however, there was a significant increase in patients achieving mRS score 0–3 (MRI, 55.1% vs 23.9%, *P*<0.001; CT, 35.2% vs 8.3%, *P*=0.014, for reperfused vs nonreperfused, respectively) and decreased mortality among successful reperfused patients (MRI, 28.0% vs 56.5%, *P*=0.001; CT, 38.9% vs 79.2%, *P*=0.001, for reperfused vs nonreperfused, respectively).

N=1252). Peri-interventional complications tended to occur more frequently in patients with ASPECTS 0–5 (16.9% versus 12.2%; *P*=0.058), but no specific type of complication was more likely (Table V in the online-only Data Supplement). Rates of sICH were comparable between patients with ASPECTS 0–5 and ASPECTS 6–10 (7.2% versus 6.0%; *P*=0.466). Patients with ASPECTS 0–5 had significantly lower rates of favourable outcome (mRS score, 0–3; 40.1% versus 61.2%; *P*<0.001, Figure IX in the online-only Data Supplement) and a doubled mortality (40.9% versus 21.2%; *P*<0.001) compared with those with ASPECTS 6–10. However, the relative merits of achieving successful reperfusion was comparable, as indicated by comparable adjusted Odds Ratios (Figure 3). No evidence for an interaction between successful reperfusion

Table 2. Output of Logistic Regression Model After Adjustment for Confounders (ASPECTS 0–5)

ASPECTS 0–5 N=237	N Included Into Regression	aOR TICI 2b/3	95% CI	*P* Value	*P* Value for Interaction With Age (≤70 vs >70)	*P* Value for Interaction With MRI vs CT
Primary						
mRS score 0–3	221/237	5.534	2.363–12.961	<0.001	0.125	0.580
Secondary						
mRS score 0–2	221/237	5.583	1.964–15.873	0.001*	0.891	0.998
sICH	220/237	0.235	0.062–0.887	0.033†	0.181	0.690
Mortality	221/237	0.180	0.083–0.390	<0.001*	0.332	0.662
Major early neurological improvement	144/237	6.627	1.361–32.276	0.019†	0.063	0.998

aOR indicates adjusted odds ratio; ASPECTS, Alberta Stroke Program Early CT Score; CT, computed tomography; MRI; magnetic resonance imaging; mRS, modified Rankin Scale; and sICH, symptomatic intracerebral hemorrhage.

**P*<0.01.

†*P*<0.05.

Table 3. Output of Logistic Regression Model After Adjustment for Confounders (ASPECTS 0–4)

ASPECTS 0–4 N=144	N Included Into Regression	aOR TICI 2b/3	95% CI	*P* Value	*P* Value for Interaction With Age (≤70 vs >70)	*P* Value for Interaction With MRI vs CT
Primary						
mRS score 0–3	133/144	2.589	0.858–7.816	0.091	0.140	0.998
Secondary						
mRS score 0–2	133/144	3.971	0.951–16.585	0.059	0.958	0.998
sICH	132/144	0.285	0.053–1.541	0.145	0.164	0.773
Mortality	133/144	0.168	0.056–0.499	0.001*	0.346	0.998
Major early neurological improvement	89/144	11.621	0.760–177.690	0.078	0.071	0.999

aOR indicates adjusted odds ratio; ASPECTS, Alberta Stroke Program Early CT Score; CT, computed tomography; MRI; magnetic resonance imaging; mRS, modified Rankin Scale; and sICH, symptomatic intracerebral hemorrhage.

**P*<0.01.

and ASPECTS 0–5 versus ASPECTS 6–10 was observed for all outcomes (Figure 3).

Discussion

Whether ischemic stroke patients presenting with low ASPECTS should be treated with mechanical thrombectomy is currently one of the most relevant unanswered question in acute stroke treatment. There were 4 major findings in our retrospective subgroup analysis derived from a large multicenter retrospective registry: (1) In patients with ASPECTS 0–5, successful reperfusion—at best TICI 3[14,15]—showed a robust association with better functional outcome, lower mortality and fewer sICH. (2) These effects remained significant after adjusting for imaging modality-associated variance, but were less marked in patients presenting with ASPECTS 0–4, where only the effect on mortality remained significant. (3) As anticipated, patients with ASPECTS 0–5 had a significantly worse clinical course than patients with ASPECTS 6–10. (4) Interventions led to less successful reperfusion and tended to be more complicated in patients with ASPECTS 0–5 than in patients with ASPECTS 6–10, but rates of sICH were comparable.

In our multicenter registry, 15.5% (237/1532) of patients with endovascularly treated large-vessel occlusion anterior circulation strokes presented with ASPECTS 0–5. The proportion of patients treated with low ASPECTS scores differed significantly between participating centers, supporting the notion that treatment decisions regarding this subgroup vary widely. Only ≈10% of patients included in the HERMES collaborative

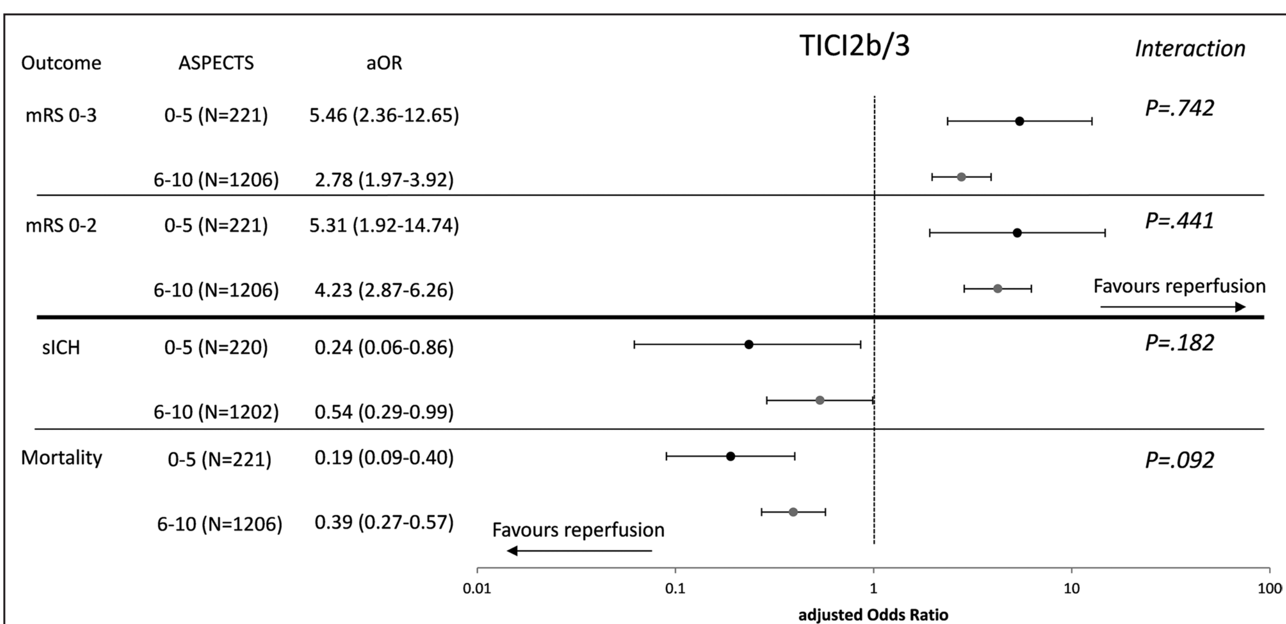

Figure 3. Effect of successful reperfusion in patients with ASPECTS 0–5 (Alberta Stroke Program Early CT Score) and patients with ASPECTS 6–10. Adjusted odds ratios were calculated in both subgroups using multivariable binary logistic regression adjusting for age, sex, admission National Institutes of Health Stroke Scale (NIHSS), tandem lesion, center, intravenous thrombolysis, risk factor hypertension, risk factor dyslipidemia, risk factor smoking, risk factor previous stroke, risk factor diabetes mellitus, in-hospital stroke, type of admission imaging, intracranial ICA/carotid-T vs M1/M2. Interaction was tested repeating the analysis in all patients and implementing an interaction term ASPECTS 0–5 vs ASPECTS 6–10 * TICI 2b/3. Please note that for ASPECTS 0–5 the adjusted odds ratio slightly differ from the analysis in Table 2, because the term ASPECTS 0–3 vs 4–5 was removed.

analysis presented with ASPECTS 0–5, which may partially explain the nonsignificance of the point estimate in this subgroup (OR, 1.24; 95% CI, 0.62–2.49; n=121).[1] Corroborating our findings, Mourand et al[10] showed that patients with diffusion-weighted ASPECTS 0–5 undergoing endovascular thrombectomy had better outcomes than patients who did not receive endovascular treatment. Furthermore, another recent multicenter analysis found equal rates of sICH, but better outcome in the successfully reperfused patient group (mRS score, 0–2; adjusted relative risk, 3.00; 95% CI, 1.71–5.29).[9] In the present study, which only included patients with CT or diffusion-weighted ASPECTS ≤5, we not only found better outcomes in successfully than in unsuccessfully reperfused patients but also lower rates of sICH. This observation has also been reported by others.[16] Hence, some reassurance is provided that rates of sICH will not be substantially higher if patients are reperfused endovascularly, despite abrupt restoration of blood flow into a large infarct core.

Despite the potential of more favorable results in endovascularly treated patient, the overall proportion of patients with functional independence (mRS score, 0–2) at 3 months was limited to 25% overall, and 32% when reperfusion occurred. Therefore, patients and families should be informed that acute treatment in such situations will still be associated with an important likelihood of dependency or death in the majority of patients, and other prognostic factors may be considered before a treatment decision is made. Interestingly, patients with ASPECTS 0–5 had lower recanalization rates despite equal number of thrombectomy attempts. A possible explanation may arise because of the operator's decision to stop the procedure because it was deemed futile in light of the advanced ischemic core. However, it should also be considered that there were significant differences between ASPECTS 0–5 and ASPECTS 6–10 patients regarding occlusion site distribution, frequency of underlying cervical artery dissection and stroke causes. All of the latter may also effect the occurrence of complications; hence, this observation and its interpretation as more complicated procedures should be handled with caution.

There are multiple conceivable reasons for a clinical benefit of successful reperfusion despite low ASPECTS and these are in part associated with the limitations of the ASPECTS methodology.[17] First, ASPECTS is only a mediocre surrogate for infarct volume[18] and, just like sole infarct volume, neglects the eloquence of the respective tissue, with significant differences being observed across different ASPECTS areas.[19–21] Second, some DWI-ASPECTS lesions may be reversible, especially in the first 3 hours after symptom-onset,[22,23] thus leading to overestimation of the infarct core. However, it has been shown that the clinical significance and tissue volumes associated with lesion reversal are minimal.[24,25] Third, the ASPECTS suggests a merely dichotomized course of ischemic lesions (infarcted versus not infarcted), which is likely to be not true. Several studies assessed the importance of gradually decreasing ADC values and its intralesional patterns for patients' outcome and risk of hemorrhagic transformation.[26,27] Last and according to the different ischemic tolerance of gray and white matter,[28–30] both tissue types are likely to undergo infarction at different time points. As such, white matter tracts in an ASPECTS positive (gray matter largely infarcted) region may be salvaged by rapid reperfusion,[31–34] thus overestimating the infarct core and underestimating the potential beneficial effect of successful reperfusion in this area.[31]

In general, older patients have higher odds for poor outcome, which is mostly because of more comorbidities and decreased functional reserve.[35] Corroborating this, age was found to be a major predictor in all multivariate logistic regression models applied in the ASPECTS 0–5 subgroup. Mourand et al[10] suggested that patients aged ≤70 were particularly likely to benefit from endovascular treatment when presenting with ASPECTS 0–5. We found no evidence, however, that the outcome-modifying effect of successful reperfusion differed substantially between age groups. We thus conclude that limiting endovascular treatment to younger patients with ASPECTS 0–5 does not seem to be justified by our data.

The present analysis included both patients with CT (N=78) and with diffusion-weighted (N=154) ASPECTS 0–5 (in 5 patients no information on imaging modality was available). Although diffusion-weighted ASPECTS is thought to be more sensitive in terms of detecting early ischemic changes,[6] it may also overestimate the final infarct core.[25,32] In our analysis, we did not find a significant interaction between the effect of successful reperfusion and the imaging modality on which the ASPECTS scoring was based. However, patients for whom CT was the admission imaging modality had a poorer prognosis per se. A sensitivity analysis with implementation of a 1-point increase in the diffusion-weighted ASPECTS also failed to provide evidence that the above-mentioned association between successful reperfusion and better outcome would change significantly.

Limitations

Most importantly, ASPECTS scores were rated at each center and were not core-lab adjudicated. Hence, there is uncertainty because of interrater variability. In particular, this has to be kept in mind, as the interrater agreement for DWI-ASPECTS[36] and CT-ASPECTS[37] is only modest. Our analysis, however, primarily used dichotomizations of ASPECTS 0–5, which will decrease the interrater variability to some extent.[36] Furthermore, the low ASPECTS group is primarily supplied by 3 centers, limiting generalizability of the findings. Another limitation of the ASPECTS is that it fails to account for ischemia outside the middle cerebral artery territory, such as anterior cerebral artery and posterior cerebral artery infarcts in case of carotid-T occlusions. In addition, simply adding 1 point to DWI ASPECTS may not adequately reflect the difference between CT and DWI-ASPECTS in our cohort, because the SAMURAI registry did not exclusively include large-vessel occlusion patients (22.5% with M2/M3 and 28.3 without visible occlusion) and only a few patients with low ASPECTS were included, which may alter correlation between CT and DWI ASPECTS observed in this study. Furthermore, operator-graded TICI scoring may lead to further bias (eg, because the operator tends to overestimate the success of her or his intervention). Third, a lost-to-follow-up rate of 10.1% harbors the potential of selection bias. However, lost-to-follow-up rates were lower in the ASPECTS 0–5 group, than for the ASPECTS 6–10 group (5.2% versus 10.9%; *P*=0.004) and we did not detect a systemic bias when comparing baseline parameters of patients with and without follow-up. Fourth, only patients treated endovascularly were included in this registry, which may introduce a selection bias towards patients with ASPECTS 0–5, in whom the chances of a good outcome were rated decent (according to other clinical factors, not corrected for in the multivariate analysis). Last, this analysis includes interventions with only 1 device.

In summary and because of the retrospective, nonrandomized nature of the data and the lack of an untreated control group, our results should be viewed as hypothesis generating that suggest the need of a future randomized controlled trial. However, when considering that the outcome for unsuccessfully reperfused patients resembles the natural course of the disease, and may thus partially substitute for a control group, the current analysis supports the notion that rapid and complete reperfusion in these patients is beneficial. This deduction is limited by the fact that an unsuccessful procedure may actually harm the patient by, for example, complications and sedation. Hence, formal testing of the best treatment approach (ie, mechanical thrombectomy versus best medical treatment) in randomized controlled trial is warranted and 1 has recently started recruiting patients (TENSION [Efficacy and Safety of Thrombectomy in Stroke With Extended Lesion and Extended Time Window], Clinical Trial Registration—URL: https://www.clinicaltrials.gov. Unique identifier: NCT03094715). In addition, this study highlights the potential impact of the imaging modality used for ASPECTS grading and associated outcomes of selected populations. Future trials should aim to consider these populations separately and adjust their power calculations accordingly. The results support the notions that cut-offs for treatment are likely to be not directly comparable among centers using CT or magnetic resonance imaging.

Conclusions

In the subgroup of patients presenting with ASPECTS 0–5, successful reperfusion is associated with superior outcomes and a better safety profile compared with patients in whom reperfusion was unsuccessful. The mortality reducing effect remained tangible in patients with ASPECTS 0–4. Rates of sICH were comparable between patients with ASPECTS 0–5 and those with ASPECTS 6–10, suggesting that abrupt restoration of blood flow into a large infarct after successful reperfusion does not necessarily increase the risk of sICH. The data stresses the need for a randomized controlled trial comparing the benefits of endovascular treatment versus best medical treatment in this subgroup of patients. Furthermore, the study underlines that these trials should separately assess included populations with strata of imaging modality used for selection.

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